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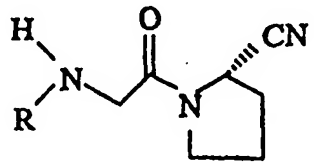
(54) Title: N–SUBSTITUTED 2–CYANOPYRROLIDINES

(57) Abstract

N–(N'–substituted glycyl)–2–cyanopyrrolidines, e.g. the compounds of formula (I) wherein R has various significances, are novel. They inhibit DPP–IV (dipeptidyl–peptidase–IV) activity. They are therefore indicated for use as pharmaceuticals in inhibiting DPP–IV and in the treatment of conditions mediated by DPP–IV, such as non–insulin–dependent diabetes mellitus, arthritis, obesity, osteoporosis and further conditions of impaired glucose tolerance.



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N-SUBSTITUTED 2-CYANOPYRROLIDINES

Field

The present invention relates to N-substituted 2-cyanopyrrolidines. More particularly, it provides novel N-glycyl-2-cyanopyrrolidine derivatives.

Background

Dipeptidyl peptidase-IV (DPP-IV) is a serine protease which cleaves N-terminal dipeptides from a peptide chain containing, preferably, a proline residue in the penultimate position. Although the biological role of DPP-IV in mammalian systems has not been completely established, it is believed to play an important role in neuropeptide metabolism, T-cell activation, attachment of cancer cells to the endothelium and the entry of HIV into lymphoid cells. DPP-IV is responsible for inactivating glucagon-like peptide-1 (GLP-1). More particularly, DPP-IV cleaves the amino-terminal His-Ala dipeptide of GLP-1, generating a GLP-1 receptor antagonist, and thereby shortens the physiological response to GLP-1. Since the half-life for DPP-IV cleavage is much shorter than the half-life for removal of GLP-1 from circulation, a significant increase in GLP-1 bioactivity (5- to 10-fold) is anticipated from DPP-IV inhibition. Since GLP-1 is a major stimulator of pancreatic insulin secretion and has direct beneficial effects on glucose disposal, DPP-IV inhibition appears to represent an attractive approach for treating non-insulin-dependent diabetes mellitus (NIDDM).

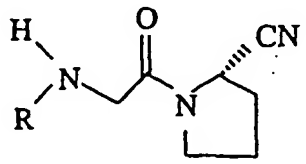
Although a number of DPP-IV inhibitors have been described, all have limitations relating to potency, stability or toxicity. Accordingly, a great need exists for novel DPP-IV inhibitors which are useful in treating conditions mediated by DPP-IV inhibition and which do not suffer from the above-mentioned limitations.

Summary of the invention

The invention provides novel N-(N'-substituted glycyl)-2-cyanopyrrolidines which are effective as DPP-IV inhibitors in treating conditions mediated by DPP-IV. It also concerns corresponding pharmaceutical compositions, a process for their preparation, a method of inhibiting DPP-IV comprising administering to a patient in need of such treatment a therapeutically effective amount thereof, the compounds for use as a pharmaceutical, and their use in a process for the preparation of a medicament for treating a condition mediated by DPP-IV.

Detailed description

The invention concerns N-(N'-substituted glycyl)-2-cyanopyrrolidines, hereinafter briefly named "**the compounds of the invention**"; more particularly, it concerns compounds of formula I:



I

wherein **R** is:

a) $R_1R_{1a}N(CH_2)_m$- wherein

R_1 is a pyridinyl or pyrimidinyl moiety optionally mono- or independently disubstituted with (C_{1-4})alkyl, (C_{1-4})alkoxy, halogen, trifluoromethyl, cyano or nitro; or phenyl optionally mono- or independently disubstituted with (C_{1-4})alkyl, (C_{1-4})alkoxy or halogen;

R_{1a} is hydrogen or (C_{1-8})alkyl; and

m is 2 or 3;

b) (C_{3-12})**cycloalkyl** optionally monosubstituted in the 1-position with (C_{1-3})hydroxyalkyl;

c) $R_2(CH_2)_n$- wherein either

R_2 is phenyl optionally mono- or independently di- or independently trisubstituted with (C_{1-4})alkyl, (C_{1-4})alkoxy, halogen or phenylthio optionally monosubstituted in the phenyl ring with hydroxymethyl; or is (C_{1-8})alkyl; a [3.1.1]bicyclic carbocyclic moiety optionally mono- or plurisubstituted with (C_{1-8})alkyl;

a pyridinyl or naphthyl moiety optionally mono- or independently disubstituted with (C_{1-4})alkyl, (C_{1-4})alkoxy or halogen; cyclohexene; or adamantyl; and

n is 1 to 3; or

R_2 is phenoxy optionally mono- or independently disubstituted with (C_{1-4})alkyl, (C_{1-4})alkoxy or halogen; and

n is 2 or 3;

d) $(R_3)_2CH(CH_2)_2$- wherein each R_3 independently is phenyl optionally mono- or independently disubstituted with (C_{1-4})alkyl, (C_{1-4})alkoxy or halogen;

e) $R_4(CH_2)_p$- wherein R_4 is 2-oxopyrrolidinyl or (C_{2-4})alkoxy and

p is 2 to 4;

f) isopropyl optionally monosubstituted in 1-position with (C_{1-3})hydroxyalkyl;

g) R_5 wherein R_5 is: indanyl; a pyrrolidinyl or piperidinyl moiety optionally substituted with benzyl; a [2.2.1]- or [3.1.1]bicyclic carbocyclic moiety optionally mono- or plurisubstituted with (C_{1-8})alkyl; adamantyl; or (C_{1-8})alkyl optionally mono- or independently plurisubstituted with hydroxy, hydroxymethyl or phenyl optionally mono- or independently disubstituted with (C_{1-4})alkyl, (C_{1-4})alkoxy or halogen;

in free form or in acid addition salt form.

The compounds of formula I can exist in free form or in acid addition salt form. Salt forms may be recovered from the free form in known manner and vice-versa. Acid addition salts may e.g. be those of pharmaceutically acceptable organic or inorganic acids. Although the preferred acid addition salts are the hydrochlorides, salts of methanesulfonic, sulfuric, phosphoric, citric, lactic and acetic acid may also be utilized.

The compounds of the invention may exist in the form of optically active isomers or diastereoisomers and can be separated and recovered by conventional techniques, such as chromatography.

"Alkyl" and "alkoxy" are either straight or branched chain, of which examples of the latter are isopropyl and tert-butyl.

R preferably is a), b) or e) as defined above. R_1 preferably is a pyridinyl or pyrimidinyl moiety optionally substituted as defined above. R_{1a} preferably is hydrogen. R_2 preferably is phenyl optionally substituted as defined above. R_3 preferably is unsubstituted phenyl.

R_4 preferably is alkoxy as defined above. R_5 preferably is optionally substituted alkyl as defined above. m preferably is 2. n preferably is 1 or 2, especially 2. p preferably is 2 or 3, especially 3.

Pyridinyl preferably is pyridin-2-yl; it preferably is unsubstituted or monosubstituted, preferably in 5-position. Pyrimidinyl preferably is pyrimidin-2-yl. It preferably is unsubstituted or monosubstituted, preferably in 4-position. Preferred as substitutents for pyridinyl and pyrimidinyl are halogen, cyano and nitro, especially chlorine.

When it is substituted, phenyl preferably is monosubstituted; it preferably is substituted with halogen, preferably chlorine, or methoxy. It preferably is substituted in 2-, 4- and/or 5-position, especially in 4-position.

(C_{3-12})cycloalkyl preferably is cyclopentyl or cyclohexyl. When it is substituted, it preferably is substituted with hydroxymethyl. (C_{1-4})alkoxy preferably is of 1 or 2 carbon atoms, it especially is methoxy. (C_{2-4})alkoxy preferably is of 3 carbon atoms, it especially is isopropoxy. Halogen is fluorine, chlorine, bromine or iodine, preferably fluorine, chlorine or bromine, especially chlorine. (C_{1-8})alkyl preferably is of 1 to 6, preferably 1 to 4 or 3 to 5, especially of 2 or 3 carbon atoms, or methyl. (C_{1-4}) alkyl preferably is methyl or ethyl, especially methyl. (C_{1-3})hydroxyalkyl preferably is hydroxymethyl.

A [3.1.1]bicyclic carbocyclic moiety optionally substituted as defined above preferably is bicyclo[3.1.1]hept-2-yl optionally disubstituted in 6-position with methyl, or bicyclo[3.1.1]hept-3-yl optionally trisubstituted with one methyl in 2-position and two methyl groups in 6-position. A [2.2.1]bicyclic carbocyclic moiety optionally substituted as defined above preferably is bicyclo[2.2.1]hept-2-yl.

Naphthyl preferably is 1-naphthyl. Cyclohexene preferably is cyclohex-1-en-1-yl. Adamantyl preferably is 1- or 2-adamantyl.

A pyrrolidinyl or piperidinyl moiety optionally substituted as defined above preferably is pyrrolidin-3-yl or piperidin-4-yl. When it is substituted it preferably is N-substituted.

A preferred group of compounds of the invention is the compounds of formula I wherein R is R' (**compounds Ia**), whereby R' is:

- R_1'$NH(CH_2)_2$- wherein R_1' is pyridinyl optionally mono- or independently disubstituted with halogen, trifluoromethyl, cyano or nitro; or unsubstituted pyrimidinyl;
- (C_{3-7})cycloalkyl optionally monosubstituted in 1-position with (C_{1-3})hydroxyalkyl;
- R_4'$(CH_2)_3$- wherein R_4' is (C_{2-4})alkoxy; or
- R_5, wherein R_5 is as defined above;

in free form or in acid addition salt form.

More preferred compounds of the invention are those compounds of formula I wherein R is R'' (**compounds Ib**), whereby R'' is:

- R_1''$NH(CH_2)_2$- wherein R_1'' is pyridinyl mono- or independently disubstituted with halogen, trifluoromethyl, cyano or nitro;
- (C_{4-6})cycloalkyl monosubstituted in 1-position with (C_{1-3})hydroxyalkyl;
- R_4'$(CH_2)_3$- wherein R_4' is as defined above; or
- R_5' wherein R_5' is a [2.2.1]- or [3.1.1]bicyclic carbocyclic moiety optionally mono- or plurisubstituted with (C_{1-8})alkyl; or adamantyl;

in free form or in acid addition salt form.

Even more preferred compounds of the invention are the compounds of formula I wherein R is R''' (**compounds Ic**), whereby R''' is:

- R_1''$NH(CH_2)_2$- wherein R_1'' is as defined above;
- (C_{4-6})cycloalkyl monosubstituted in 1-position with hydroxymethyl;
- R_4'$(CH_2)_3$- wherein R_4' is as defined above; or
- R_5'' wherein R_5'' is adamantyl;

in free form or in acid addition salt form.

A further group of compounds of the invention is **compounds Ip**, wherein R is R^p, which is:

a) $R_1^pNH(CH_2)_2$- wherein R_1^p is a pyridinyl or pyrimidinyl moiety optionally mono- or independently disubstituted with halogen, trifluoromethyl, cyano or nitro;

b) (C_{3-7})cycloalkyl optionally monosubstituted in 1-position with (C_{1-3})hydroxyalkyl;

c) $R_2^p(CH_2)_2$- wherein R_2^p is phenyl optionally mono- or independently di- or independently trisubstituted with halogen or (C_{1-3})alkoxy;

d) $(R_3^p)_2CH(CH_2)_2$- wherein each R_3^p independently is phenyl optionally monosubstituted with halogen or (C_{1-3})alkoxy;

e) $R_4(CH_2)_3$- wherein R_4 is as defined above; or

f) isopropyl optionally monosubstituted in 1-position with (C_{1-3})hydroxyalkyl;

in free form or in pharmaceutically acceptable acid addition salt form.

A further group of compounds of the invention is **compounds Is**, wherein R is R^s, which is:

a) $R_1^sR_{1a}^s(CH_2)_{ms}$- wherein R_1^s is pyridinyl optionally mono- or independently disubstituted with chlorine, trifluoromethyl, cyano or nitro; pyrimidinyl optionally monosubstituted with chlorine or trifluoromethyl; or phenyl;

R_{1a}^s is hydrogen or methyl; and

ms is 2 or 3;

b) (C_{3-12})cycloalkyl optionally monosubstituted in 1-position with hydroxymethyl;

c) $R_2^s(CH_2)_{ns}$- wherein either

R_2^s is phenyl optionally mono- or independently di- or independently trisubstituted with halogen, alkoxy of 1 or 2 carbon atoms or phenylthio monosubstituted in the phenyl ring with hydroxymethyl; (C_{1-6})alkyl; 6,6-dimethylbicyclo[3.1.1]hept-2-yl; pyridinyl; naphthyl; cyclohexene; or adamantyl; and ns is 1 to 3; or

R_2^s is phenoxy; and ns is 2;

d) (3,3-diphenyl)propyl;

e) $R_4'(CH_2)_{ps}$ wherein R_4' is 2-oxopyrrolidin-1-yl or isopropoxy and

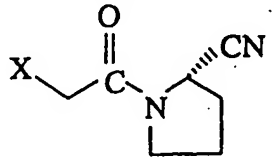
ps is 2 or 3;

f) isopropyl optionally monosubstituted in 1-position with hydroxymethyl;

g) R_5' wherein R_5' is: indanyl; a pyrrolidinyl or piperidinyl moiety optionally N-substituted with benzyl; bicyclo[2.2.1]hept-2-yl; 2,6,6-trimethylbicyclo-[3.1.1]hept-3-yl; adamantyl; or (C_{1-8})alkyl optionally mono- or independently disubstituted with hydroxy, hydroxymethyl or phenyl;

in free form or in acid addition salt form.

The compounds of the invention may be prepared by a process which comprises coupling a reactive (2-cyanopyrrolidino)carbonylmethylene compound with an appropriate substituted amine; more particularly, for the preparation of the compounds of formula I it comprises reacting a compound of formula II



II

wherein X is a reactive group,

with a compound of formula III

NH_2R III

wherein R is as defined above,

and recovering the resultant compound of formula I in free form or in acid addition salt form.

X preferably is a halogen such as bromine, chlorine or iodine.

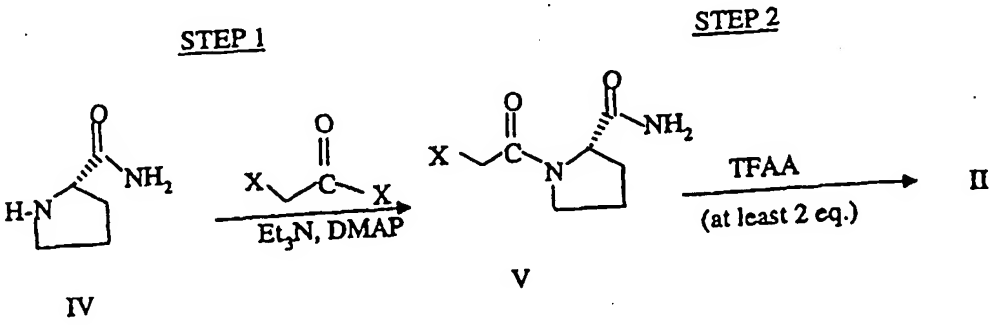
The process of the invention may be effected in conventional manner.

The compound of formula II is preferably reacted with at least 3 equivalents of a primary amine of formula III. The reaction is conveniently conducted in the presence of an inert, organic solvent, preferably a cyclic ether such as tetrahydrofuran. The temperature preferably is of from about 0° to about 35°C, preferably between about 0° and about 25°C.

The compounds of the invention may be isolated from the reaction mixture and purified in conventional manner, e.g. by chromatography.

The starting materials may also be prepared in conventional manner.

The compounds of formula II may e.g. be prepared by the following two-step reaction scheme:



Step 1 involves the reaction of the pyrrolidine of formula IV with a slight molar excess of a haloacetylhalide such as bromoacetylbromide or chloroacetylchloride and triethylamine and a catalytic amount of dimethylaminopyridine (DMAP). The reaction conveniently is conducted in the presence of an inert, organic solvent, preferably a chlorinated, aliphatic hydrocarbon such as methylene chloride, at a temperature of from about 0° to about 25°C, preferably at a temperature between about 0° and about 15°C.

Step 2 concerns the dehydration of the compound of formula V, prepared in Step 1, with at least 2 equivalents of trifluoroacetic anhydride (TFAA). The dehydration preferably is conducted in the presence of an inert, organic solvent such as tetrahydrofuran or a chlorinated, aliphatic hydrocarbon such as methylene chloride, at a temperature of from about 0° to about 25°C, preferably at a temperature between about 0° and about 15°C.

Insofar as its preparation is not particularly described herein, a compound used as starting material is known or may be prepared from known compounds in known manner or analogously to known methods or analogously to methods described in the Examples.

The following Examples illustrate the invention. All temperatures are in degrees Celsius.

Example 1: 1-[2-[(5-Chloropyridin-2-yl)amino]ethylamino]acetyl-2-cyano-(S)-pyrrolidine

To a 500 ml flask is added 16.6 g of 2-[(5-chloropyridin-2-yl)amino]ethylamine and 100 ml of tetrahydrofuran and the mixture is cooled in an ice bath. To the cooled mixture is added 7.0 g of (2-cyanopyrrolidino)carbonylmethylene-(S)-bromide dissolved in 30 ml of tetrahydrofuran. The resultant mixture is stirred for 2 hours at 0°, the solvent is removed by rotovaping and the mixture is partitioned between ethyl acetate and water. The product is then extracted into the ethyl acetate layer and the aqueous layer is then washed twice with ethyl acetate. The combined organic layers are washed successively with water and brine, dried over sodium sulfate and concentrated to obtain the desired free base compound in crude form. The crude form is then purified on silica gel employing a mixture of 5% methanol in methylene chloride as the eluent to yield the title compound in free base form as a light brown oil.

After dissolving the free base in 30 ml of dry tetrahydrofuran, hydrogen chloride gas is bubbled into the solution for five seconds. The off-white precipitate that forms is filtered, washed with dry tetrahydrofuran and the solvent is removed by high vacuum pumping to obtain the title compound in dihydrochloride acid addition salt form (off-white solid; m.p. 265°-267°; NMR: see * at bottom of Table hereunder).

The starting material is obtained as follows:

a) 22.37 g of (S)-2-carbamoylpyrrolidine, 30.1 ml of triethylamine and 30.0 mg of dimethylaminopyridine (DMAP) are dissolved in 200 ml of methylene chloride and the solution is then added, dropwise, to an ice-cold solution of 18.8 ml of bromoacetylbromide in 192 ml of methylene chloride, over a period of 60 minutes under a calcium sulfate drying tube. The resultant solution is stirred for 2 hours at ice-water temperature under a calcium sulfate drying tube, then poured into 3.5 liters of ethyl acetate. The resultant precipitate is filtered, washed with ethyl acetate, and the filtrate is concentrated to obtain (2-carbamoylpyrrolidino)-carbonylmethylene-(S)-bromide (hard yellow taffy).

b) 50.0 g of the **bromide compound** prepared in a) above is dissolved in 300 ml of methylene chloride and the solution is cooled in an ice water bath under a calcium sulfate drying tube. The cooled solution is then poured into 60.2 ml of **trifluoroacetic anhydride** over a 2 minute period, the resultant solution is stirred at ice-water temperature under a calcium sulfate drying tube for 4 hours, and partitioned between methylene chloride and saturated aqueous sodium bicarbonate. The product is extracted into the methylene chloride layer and the aqueous layer is washed twice with methylene chloride. The combined organic layers are washed successively with water and brine and then dried over sodium sulfate. The solution is filtered and the solvent is removed by rotovaping and high vacuum pumping to obtain **(2-cyanopyrrolidino)carbonylmethylene-(S)-bromide** (dark yellow solid).

The following compounds of the invention, of formula I, are obtained in analogous manner by reacting a corresponding compound of formula II with a corresponding compound of formula III (in the following Table, where only an acid addition salt form of a compound of the invention is mentioned, the compound is recovered from the free base without isolation thereof):

Example No.	R	Form	Analogously to Ex. No.	Characterization data
2	2-[(5-CF_3-pyridin-2-yl)amino]ethyl	b	1[1)]	golden oil; NMR*
3	2-[(5-cyanopyridin-2-yl)amino]ethyl	b	1	golden oil
		dch	1	off-white precipitate, m.p. 155-157°; NMR*; $[\alpha]_D^{20}$= - 77.2° (c=0.012, MeOH)
4	2-[(pyrimidin-2-yl)amino]ethyl	b	2[1a)]	golden oil; NMR*
5	(1-hydroxymethyl)cyclopent-1-yl	b	1[2)]	yellow solid; m.p. 65-67°; NMR*
6	2-[(pyridin-2-yl)amino]ethyl	b	2[3)]	golden oil; NMR*
7A	2-[(4-chloropyrimidin-2-yl)amino]ethyl	b	2	tan solid; NMR*
7B	2-[(3-chloropyridin-2-yl)amino]ethyl	b	2	golden oil; NMR*
7C	2-[(4-CF_3-pyrimidin-2-yl)amino]ethyl	b	2	golden oil; NMR*
7D	2-(2-chlorophenyl)ethyl	b	2	NMR*
7E	(3,3-diphenyl)propyl	b	2	NMR*
8	2-[(5-nitropyridin-2-yl)amino]ethyl	b	5[3a)]	bright yellow thick oil; NMR*
9A	2-[(3-chloro-5-CF_3-pyridin-2-yl)amino]ethyl	b	2[3b)]	golden oil; NMR*
9B	2-[(3-CF_3-pyridin-2-yl)amino]ethyl	b	2[3b)]	golden oil; NMR*
9C	2-[(3,5-dichloropyridin-2-yl)amino]ethyl	b	2[3b)]	golden oil; NMR*
10	cyclopent-1-yl	b	2	tan solid
		ch	1	white solid; NMR*
11	2-(2-bromo-4,5-dimethoxyphenyl)ethyl	b	5[3a)]	clear light yellow, thick oil; NMR*
12	3-(isopropoxy)propyl	b	1	brown oil
		ch	1	white solid, m.p. 174-176°; NMR*

Example No.	R	Form	Analogously to Ex. No.	Characterization data
13	2-hydroxy-1,1-dimethylethyl	b	2[4]	golden oil
		ch	1	brown solid; NMR*
14	3-(2-oxopyrrolidin-1-yl)propyl	b	2[5]	golden oil
		ch	1	tan solid; NMR*
15	1-hydroxymethylcyclohexyl	b	1[6]	yellow waxy solid; m.p. 93°; ^{13}C-NMR: 118.1 (ppm)
16	2-(4-ethoxyphenyl)ethyl	ch	1	white solid; m.p. 182-184°; ^{13}C-NMR: 121.4 (ppm)
17	1-phenylmethyl-3-(R)-pyrrolidinyl	dch	1[7]	off-white solid; m.p. 175-177°; ^{13}C-NMR: 121.5 (ppm)
18	2-(4-methoxyphenyl)ethyl	ch	1	white solid; m.p. 185-187°; ^{13}C-NMR: 121.4 (ppm)
19	2-(3-methoxyphenyl)ethyl	ch	1	light yellow solid; m.p. 172-174°; ^{13}C-NMR: 119.25 (ppm)
20	(1-naphthalenyl)methyl	ch	1	light yellow solid; m.p. 130-135°; ^{13}C-NMR: 119.29 (ppm)
21	3-phenylpropyl	dch	1	off-white fluffy solid; ^{13}C-NMR: 119.26 (ppm)
22	3-[(phenyl)(methyl)amino]propyl	ch	1	white solid; m.p. 96-98° (foams); ^{13}C-NMR: 121.6 (ppm)
23	2-(3,4-dimethoxyphenyl)ethyl	ch	1	white solid; m.p. 170-172°; ^{13}C-NMR: 121.5 (ppm)
24	cycloheptyl	ch	1	white solid; m.p. 68-70°; ^{13}C-NMR: 121.4 (ppm)
25	[1S[1α,2α(S*),5α]]-(6,6-dimethylbicyclo[3.1.1]-hept-2-yl)methyl	ch	1[8]	white solid; m.p. 275-279° (dec.); ^{13}C-NMR: 119.17 (ppm)
26	2-(2,5-dimethoxyphenyl)ethyl	ch	1	white fluffy solid; m.p. 65-67°; ^{13}C-NMR: 119.25 (ppm)
27	2-(1-cyclohexen-1-yl)ethyl	ch	1	off-white fluffy solid; m.p.162-164°; ^{13}C-NMR: 119.27 (ppm)
28	cyclohexyl	ch	1	white fluffy solid;m.p.182-184°; ^{13}C-NMR: 119.28 (ppm)
29	[1S[1α, 2α(S*),5α]]-bicyclo[2.2.1]hept-2-yl	ch	1[9]	white solid; m.p. 98-100°; ^{13}C-NMR: 118.36 (ppm)
30	2-(2-pyridinyl)ethyl	dch	1	white solid; m.p. 95-97°; ^{13}C-NMR: 121.5 (ppm)
31	(2-phenylamino)ethyl	dch	1	white solid; m.p. 124-126°; ^{13}C-NMR: 121.4 (ppm)
32	3,3-dimethylbutyl	ch	1	white solid; m.p. 164-166°; ^{13}C-NMR: 121.5 (ppm)
33	[1S[1α,2β,3α(S*),5α]]-2,6,6-trimethylbicyclo[3.1.1]-hept-3-yl	ch	1[10]	white solid; m.p. 82-84°; ^{13}C-NMR: 121.5 (ppm)

Example No.	R	Form	Analogously to Ex. No.	Characterization data
34	[S,S]-(1-hydroxymethyl)propyl	ch	1[11]	off-white solid; m.p. 80-82°; ^{13}C-NMR: 118.2 (ppm)
35	[2-[(2-hydroxymethyl)phenyl]thio]phenylmethyl	ch	1[12]	yellow solid; m.p. 65-67°; ^{13}C-NMR: 121.4 (ppm)
36	2-(2-methoxyphenyl)ethyl	ch	1	off-white solid; m.p. 174-176°; ^{13}C-NMR: 121.7 (ppm)
37	5-hydroxypentyl	ch	1	sticky light-green solid; ^{13}C-NMR: 121.67 (ppm)
38	cyclobutyl	ch	1	off-white solid; m.p. 274-278° (dec.); ^{13}C-NMR: 121.64 (ppm)
39	2-(2,4-dichlorophenyl)ethyl	ch	1	white fluffy solid;m.p.154-156°; ^{13}C-NMR: 121.48 (ppm)
40	1-(S)-(+)-hydroxymethyl-3-methylbutyl	ch	1[13]	light yellow solid; m.p. 65-66°; ^{13}C-NMR: 117.99 (ppm)
41	[1R*,2S*]-2-hydroxy-2-phenylethyl	ch	1[14]	light yellow solid; m.p. 82-83°; ^{13}C-NMR: 118.35 (ppm)
42	2-(2-fluorophenyl)ethyl	ch	1	white fluffy solid;m.p.160-162°; ^{13}C-NMR: 121.70 (ppm)
43	cyclopropyl	ch	1	off-white solid; m.p. 170-172°; ^{13}C-NMR: 121.62 (ppm)
44	[1S[1S,2S,3S,5R]]-2,6,6-trimethylbicyclo-[3.1.1]hept-3-yl	ch	1[15]	white solid; m.p. 84-86°; ^{13}C-NMR: 121.8 (ppm)
45	(2-phenoxy)ethyl	ch	1	sticky golden solid; ^{13}C-NMR: 121.7 (ppm)
46	2-(3,5-dimethoxyphenyl)ethyl	ch	1	white fluffy solid; m.p. 74-76°; ^{13}C-NMR: 121.66 (ppm)
47	1-adamantyl	ch	1	white solid; m.p. 240-242°; ^{13}C-NMR: 121.80 (ppm)
48	1,1,3,3-tetramethylbutyl	ch	1	white fluffy solid; m.p. 68-70°; ^{13}C-NMR: 121.55 (ppm)
49	2-adamantyl	ch	1	off-white solid; m.p. 122-124°; ^{13}C-NMR: 121.69 (ppm)
50	1,1-dimethylpropyl	ch	1	white fluffy solid; m.p. 62-64°; ^{13}C-NMR: 121.53 (ppm)
51	benzyl	ch	1	white solid; m.p. 58-60°; ^{13}C-NMR: 121.38 (ppm)
52	1,1-dimethylethyl	ch	1	white solid; m.p. 226-228°; ^{13}C-NMR: 121.56 (ppm)
53	(2-adamantyl)methyl	ch	1	white solid; m.p. 158-160°; ^{13}C-NMR: 121.53 (ppm)
54	2-phenylethyl	ch	1	white solid; m.p. 275-280° (dec.); ^{13}C-NMR: 121.52 (ppm)
55	pentyl	ch	1	white solid; m.p. 176-178°; ^{13}C-NMR: 121.67 (ppm)
56	butyl	ch	1	white solid; m.p. 180-182°; ^{13}C-NMR: 121.53 (ppm)

Example No.	R	Form	Analogously to Ex. No.	Characterization data
57	cyclododecyl	ch	1	white fluffy solid; ^{13}C-NMR: 121.52 (ppm)
58	cyclooctyl	ch	1	white fluffy solid; ^{13}C-NMR: 121.64 (ppm)
59	propyl	ch	1	white solid; m.p. 193-194°; ^{13}C-NMR: 121.57 (ppm)
60	ethyl	ch	1	off-white sticky solid; ^{13}C-NMR: 121.67 (ppm)
61	heptyl	ch	1	white solid; m.p. 170-172°; ^{13}C-NMR: 121.7 (ppm)
62	hexyl	ch	1	white solid; m.p. 174-176°; ^{13}C-NMR: 121.75 (ppm)
63	3-[(5-cyano-2-pyridinyl)amino]propyl	dch	1[16)]	white sticky solid; m.p. 210-212°; ^{13}C-NMR: 119.33 (ppm)
64	1-ethylpropyl	ch	1	white fluffy sticky solid; ^{13}C-NMR: 119.35 (ppm)
65	2,3-dihydro-1H-inden-2-yl	ch	1	white solid; m.p. 182-184°; ^{13}C-NMR: 121.38 (ppm)
66	1-benzylpiperidin-4-yl	ch	1	white solid; m.p. 280-283° (dec.); ^{13}C-NMR: 121.39 (ppm)

b = in free base form ch= in monohydrochloride form; dch = in dihydrochloride form
dec.= decomposes; m.p.= melting point

[1)] starting from 2-[(5-trifluoromethylpyridin-2-yl)amino]ethylamine in tetrahydrofuran, using 5 % methanol in methylene chloride as eluent
[1a)]using 10 % methanol in methylene chloride as eluent
[2)] reacting (1-hydroxymethyl)cyclopentylamine in anhydrous tetrahydrofuran for 18.h at room temperature under a calcium sulfate drying tube
[3)] using methylene chloride, methanol and ammonium hydroxide 90:10:0.5 as eluent
[3a)]using flash chromatography, employing a mixture of 5 % methanol in methylene chloride as eluent
[3b)]using 3 % methanol in methylene chloride as eluent
[4)] using methylene chloride, methanol and ammonium hydroxide 80:20:1 as eluent
[5)] using methylene chloride, methanol and ammonium hydroxide 90:10:1 as eluent
[6)] reacting (1-aminocyclohexane)methanol in tetrahydrofuran with 1-chloroacetyl-2-(S)-cyanopyrrolidine (prepared from chloroacetylchloride and L-prolinamide and reaction of the resultant product with trifluoroacetic anhydride) at ice-temperature under a calcium sulfate drying tube, and purifying the reaction mixture on silicagel employing 5 % methanol in methylene chloride as eluent

[7] using (3R)-(-)-1-benzyl-3-aminopyrrolidine as starting material
[8] using (-)-cis-myrtanylamine as starting material
[9] using (+/-)-exo-2-aminonorbornane as starting material
[10] using (1R,2R,3R,5S)-(-)-isopinocampheylamine as starting material
[11] using (S)-(+)-2-amino-1-butanol as starting material
[12] using 2-(2-aminomethyl)phenylthio)benzyl alcohol as starting material
[13] using (S)-(+)-leucinol as starting material
[14] using (1R,2S)-(-)-norephedrine as starting material
[15] using (1S,2S,3S,5R)-(+)-isopinocampheylamine as starting material
[16] using 2-(3-aminopropylamino)-5-cyanopyridine as starting material

* NMR:

Compound #	^{13}C-NMR (MHz, solvent) d ppm (CN)	
Ex. 5	^{13}C NMR (75 MHz, CD_3OD)	d 119.64 ppm (CN)
Ex. 12	^{13}C NMR (75 MHz, D_2O)	d 121.63 ppm (CN)
Ex. 1	^{13}C NMR (75 MHz, D_2O)	d 121.60 ppm (CN)
Ex. 3	^{13}C NMR (75 MHz, D_2O)	d 120.42 ppm (CN)
Ex. 8	^{13}C NMR (75 MHz, DMSO)	d 119.13 ppm (CN)
Ex. 7B	^{13}C NMR (75 MHz, $CDC1_3$)	d 118.23 ppm (CN)
Ex. 9A	^{13}C NMR (75 MHz, CD_3OD)	d 119.68 ppm (CN)
Ex. 9B	^{13}C NMR (75 MHz, CD_3OD)	d 119.66 ppm (CN)

Compound #	^{13}C NMR (MHz, solvent) d ppm (CN)
Ex. 9C	^{13}C NMR (75 MHz, CD_3OD) d 119.68 ppm (CN)
Ex. 6	^{13}C NMR (75 MHz, CD_3OD) d 119.84 ppm (CN)
Ex. 7C	^{13}C NMR (75 MHz, $CDCl_3$) d 118.23 ppm (CN)
Ex. 2	^{13}C NMR (75 MHz, CD_3OD) d 119.68 ppm (CN)
Ex. 7A	^{13}C NMR (75 MHz, CD_3OD) d 119.66 ppm (CN)
Ex. 4	^{13}C NMR (75 MHz, CD_3OD) d 119.66 ppm (CN)
Ex. 10	^{13}C NMR (75 MHz, D_2O) d 121.69 ppm (CN)
Ex. 11	^{13}C NMR (75 MHz, $CDCl_3$) d 118.31 ppm (CN)
Ex. 7D	^{13}C NMR (75 MHz, CD_3OD) d 119.63 ppm (CN)
Ex. 7E	^{13}C NMR (75 MHz, CD_3OD) d 119.64 ppm (CN)
Ex. 13	^{13}C NMR (75 MHz, D_2O) d 121.52 ppm (CN)
Ex. 14	^{13}C NMR (75 MHz, D_2O) d 121.52 ppm (CN)

The compounds of the invention in free form or in pharmaceutically acceptable acid addition salt form, hereinafter briefly named "**the agents of the invention**", in particular, the compounds of formula I in free form or in pharmaceutically acceptable acid addition salt form, possess pharmacological activity. They are therefore indicated for use as pharmaceuticals.

In particular, they inhibit DPP-IV. This activity may be demonstrated employing the **Caco-2 DPP-IV assay**, which measures the ability of test compounds to inhibit DPP-IV activity from human colonic carcinoma cell extracts. The human colonic carcinoma cell line Caco-2 can be obtained from the American Type Culture Collection (ATCC HTB 37). Differentiation of the cells to induce DPP-IV expression is accomplished as described by Reisher et al. in Proc.Natl.Acad.Sci.USA 90 (1993) 5757-5761. Cell extract is prepared from cells solubilized in 10 mM Tris-HCl, 0.15 M NaCl, 0.04 t.i.u. (trypsin inhibitor unit) aprotinin, 0.5% non-ionic detergent P40, pH 8.0, which is centrifuged at 35 000 g for 30 min at 4°C to remove cell debris. The assay is conducted by adding 20 mg solubilized Caco-2 protein, diluted to a final volume of 125 ml in assay buffer (25 mM Tris-HCl pH 7.4, 140 mM NaCl, 10 mM KCl, 1% bovine serum albumin) to microtiter plate wells. The reaction is initiated by adding 25ml of 1 mM substrate (H-Alanine-Proline-pNA; pNA is *p*-nitroaniline). The reaction is run at room temperature for 10 minutes after which time a 19 ml volume of 25% glacial acetic acid is added to stop the reaction. Test compounds are typically added as 30 ml additions and the assay buffer volume is reduced to 95 ml. A standard curve of free *p*-nitroaniline is generated using 0-500 mM solutions of free pNA in assay buffer. The curve generated is linear and is used for interpolation of substrate consumption (catalytic activity in nmoles substrate cleaved /min). The endpoint is determined by measuring absorbance at 405 nm in a Molecular Devices UV Max microtiter plate reader. The potency of the test compounds as DPP-IV inhibitors, expressed as IC_{50}, is calculated from 8-point, dose-response curves using a 4-parameter logistic function.

In the above test, IC_{50} values of from about 10 nM to about 900 nM are obtained with the agents of the invention, e.g. 22 nM for the agent of Example 3.

The DPP-IV inhibition may also be demonstrated by measuring the effects of test compounds on DPP-IV activity in human and rat plasma employing a modified version of the assay described by Kubota et al. in Clin.Exp.Immunol. 89 (1992) 192-197. Briefly, five ml of plasma are added to 96-well flat-bottom microtiter plates (Falcon), followed by the addition

of 5 ml of 80 mM $MgCl_2$ in incubation buffer (25 mM HEPES, 140 mM NaCl, 1 % RIA-grade BSA, pH 7.8). After a 5 min incubation at room temperature, the reaction is initiated by the addition of 10 ml of incubation buffer containing 0.1 mM substrate (H-Glycine-Proline-AMC; AMC is 7-amino-4-methylcoumarin). The plates are covered with aluminum foil (or kept in the dark) and incubated at room temperature for 20 min. After the 20 min reaction, fluorescence is measured using a CytoFluor 2350 fluorimeter (Excitation 380 nm Emission 460 nm; sensitivity setting 4). Test compounds are typically added as 2 ml additions and the assay buffer volume is reduced to 13 ml. A fluorescence-concentration curve of free AMC is generated using 0-50 mM solutions of AMC in assay buffer. The curve generated is linear and is used for interpolation of substrate consumption (catalytic activity in nmoles substrate cleaved/min). As with the previous assay, the potency of the test compounds as DPP-IV inhibitors, expressed as IC_{50}, is calculated from 8-point, dose-response curves using a 4 parameter logistic function.

In the above assay, IC_{50} values of from about 7 nM to about 2000 nM are obtained in human plasma, and of from about 3 nM to about 400 nM in rat plasma, e.g., for the agent of Example 3, of 7 nM in human and 6 nM in rat plasma, respectively.

In view of their ability to inhibit DPP-IV, the agents of the invention are indicated for use in treating conditions mediated by DPP-IV. It is expected that the compounds disclosed herein are useful in the treatment of non-insulin-dependent diabetes mellitus, arthritis, obesity, and osteoporosis such as calcitonin-osteoporosis. The agents of the invention improve early insulin response to an oral glucose challenge and, therefore, are particularly indicated for use in treating non-insulin-dependent diabetes mellitus and further conditions of impaired glucose tolerance (IGT).

The ability of the agents of the invention to improve early insulin response to an oral glucose challenge may e.g. be measured in insulin resistant rats according to the following method:

Male Sprague-Dawley rats that have been fed a high fat diet (saturated fat = 57 % calories) for 2-3 weeks are fasted for approximately 2 hours on the day of testing, divided into groups of 8-10, and dosed orally with 10 mmol/kg of the test compounds in carboxymethylcellulose (CMC). An oral glucose bolus of 1 g/kg is administered 30 min after

the test compound directly into the stomach of the test animals. Blood samples, obtained at various timepoints from chronic jugular vein catheters are analyzed for plasma glucose and immunoreactive insulin (IRI) concentrations, and plasma DPP-IV activity. Plasma insulin levels are assayed by a double antibody radioimmunoassay (RIA) method using a specific anti-rat insulin antibody from Linco Research (St. Louis, MO, USA). The RIA has a lower limit of detection of 0.5 mU/ml with intra- and inter-assay variations of less than 5%. Data are expressed as % increase of the mean of the control animals.

It was found that upon oral administration, each of the compounds tested amplified the early insulin response which led to an improvement in glucose tolerance in the insulin resistant test animals. The following results were obtained:

Compound	Increase of insulin response at 10 mmol/kg
Ex. 1	61 %
Ex. 3	66 %
Ex. 5	108 %
Ex. 8	144 %
Ex. 12	59 %

The precise dosage of the agents of the invention to be employed for treating conditions mediated by DPP-IV inhibition depends upon several factors, including the host, the nature and the severity of the condition being treated, the mode of administration and the particular compound employed. However, in general, conditions mediated by DPP-IV inhibition are effectively treated when an agent of the invention is administered enterally, e.g. orally, or parenterally, e.g. intravenously, preferably orally, at a daily dosage of from about 0.002 mg/kg to about 5 mg/kg, preferably of from about 0.02 mg/kg to about 2.5 mg/kg body weight or, for most larger primates, a daily dosage of from about 0.1 mg to about 250 mg, preferably from about 1 mg to about 100 mg. A typical oral dosage unit is from about 0.01 mg/kg to about 0.75 mg/kg, one to three times a day. Usually, a small dose is administered initially and the dosage is gradually increased until the optimal dosage for the host

under treatment is determined. The upper limit of dosage is that imposed by side effects and can be determined by trial for the host being treated.

The agents of the invention may be combined with one or more pharmaceutically acceptable carriers and, optionally, one or more other conventional pharmaceutical adjuvants and administered enterally, e.g. orally, in the form of tablets, capsules, caplets, etc., or parenterally, e.g. intravenously, in the form of sterile injectable solutions or suspensions. The enteral and parenteral compositions may be prepared by conventional means.

The agents of the invention may be formulated into enteral and parenteral pharmaceutical compositions containing an amount of the active substance that is effective for treating conditions mediated by DPP-IV, such compositions in unit dosage form and such compositions comprising a pharmaceutically acceptable carrier.

Those agents of the invention which are e.g. of formula I may be administered in enantiomerically pure (S) form (e.g. ≥ 98 %, preferably ≥ 99 % pure) or together with the other enantiomer, e.g. in racemic form. The above dosage ranges are based on the compounds of formula I (excluding the amount of R enantiomer).

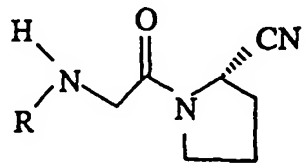
The invention thus also comprises **an agent of the invention**, in particular, a compound of formula I as defined above, in free form or in pharmaceutically acceptable acid addition salt form, **for use as a pharmaceutical**. It further includes a **pharmaceutical composition** comprising an agent of the invention, in particular a compound of formula I as defined above, in free form or in pharmaceutically acceptable acid addition salt form, together with at least one pharmaceutically acceptable carrier or diluent. It further comprises the use of an agent of the invention, in particular, a compound of formula I as defined above, in free form or in pharmaceutically acceptable acid addition salt form **in the preparation of a medicament** for inhibiting DPP-IV or treating conditions mediated by DPP-IV, by a process comprising mixing an agent of the invention with a pharmaceutically acceptable carrier or diluent. It further provides a **method of inhibiting DPP-IV, or of treating conditions mediated by DPP-IV**, which comprises administering to a patient in need of such treatment a therapeutically effective amount of a compound of the invention, in particular, of formula I in free form or in pharmaceutically acceptable acid additi n salt form.

The agents of Examples 1, 3, 5, 8 and 12 are the preferred agents of the invention, particularly those of Examples 1, 3, 5 and 12, preferably in hydrochloride acid addition salt form, especially the agent of Example 3, namely 1-[2-[(5-cyanopyridin-2-yl)amino]-ethylamino]acetyl-2-cyano-(S)-pyrrolidine, preferably in dihydrochloride acid addition salt form. It has been determined that in hydrochloride form they have an IC_{50} value in the Caco-2 DPP-IV assay of, respectively, 36, 22, 26, 8 and 279 nM, and in the modified Kubota assay above, an IC_{50} value for, respectively, human and rat plasma DPP-IV, of 27 and 22 nM (Example 1); 7 and 6 nM (Example 3); 37 and 18 nM (Example 5); 12 and 11 nM (Example 8); and 95 and 38 nM (Example 12). It is, therefore, indicated that for the above uses the compounds of Examples 1, 3, 5, 8 and 12 may be administered to larger mammals, for example humans, by similar modes of administration at similar dosages than conventionally employed with metformin.

Claims:

1. An N-(N'-substituted glycyl)-2-cyanopyrrolidine.

2. A compound of formula I:



I

wherein **R** is:

a) $R_1R_{1a}N(CH_2)_m$- wherein

R_1 is a pyridinyl or pyrimidinyl moiety optionally mono- or independently disubstituted with (C_{1-4})alkyl, (C_{1-4})alkoxy, halogen, trifluoromethyl, cyano or nitro; or phenyl optionally mono- or independently disubstituted with (C_{1-4})alkyl, (C_{1-4})alkoxy or halogen;

R_{1a} is hydrogen or (C_{1-8})alkyl; and

m is 2 or 3;

b) (C_{3-12})cycloalkyl optionally monosubstituted in the 1-position with (C_{1-3})hydroxyalkyl;

c) $R_2(CH_2)_n$- wherein either

R_2 is phenyl optionally mono- or independently di- or independently trisubstituted with (C_{1-4})alkyl, (C_{1-4})alkoxy, halogen or phenylthio optionally monosubstituted in the phenyl ring with hydroxymethyl; or is (C_{1-8})alkyl; a [3.1.1]bicyclic carbocyclic moiety optionally mono- or plurisubstituted with (C_{1-8})alkyl; a pyridinyl or naphthyl moiety optionally mono- or independently disubstituted with (C_{1-4})alkyl, (C_{1-4})alkoxy or halogen; cyclohexene; or adamantyl; and

n is 1 to 3; or

R_2 is phenoxy optionally mono- or independently disubstituted with (C_{1-4})alkyl, (C_{1-4})alkoxy or halogen; and

n is 2 or 3;

d) $(R_3)_2CH(CH_2)_2$- wherein each R_3 independently is phenyl optionally mono- or independently disubstituted with (C_{1-4})alkyl, (C_{1-4})alkoxy or halogen;

c) $R_4(CH_2)_p$- wherein R_4 is 2-oxopyrrolidinyl or (C_{2-4})alkoxy and
p is 2 to 4;

f) isopropyl optionally monosubstituted in 1-position with (C_{1-3})hydroxyalkyl;

g) R_5 wherein R_5 is: indanyl; a pyrrolidinyl or piperidinyl moiety optionally substituted with benzyl; a [2.2.1]- or [3.1.1]bicyclic carbocyclic moiety optionally mono- or plurisubstituted with (C_{1-8})alkyl; adamantyl; or (C_{1-8})alkyl optionally mono- or independently plurisubstituted with hydroxy, hydroxymethyl or phenyl optionally mono- or independently disubstituted with (C_{1-4})alkyl, (C_{1-4})alkoxy or halogen;

in free form or in acid addition salt form,

3. A compound according to claim 2 (a **compound Ip**) wherein R is R^p, which is:

a) $R_1^pNH(CH_2)_2$- wherein R_1^p is a pyridinyl or pyrimidinyl moiety optionally mono- or independently disubstituted with halogen, trifluoromethyl, cyano or nitro;

b) (C_{3-7})cycloalkyl optionally monosubstituted in 1-position with (C_{1-3})hydroxyalkyl;

c) $R_2^p(CH_2)_2$- wherein R_2^p is phenyl optionally mono- or independently di- or independently trisubstituted with halogen or (C_{1-3})alkoxy;

d) $(R_3^p)_2CH(CH_2)_2$- wherein each R_3^p independently is phenyl optionally monosubstituted with halogen or (C_{1-3})alkoxy;

e) $R_4(CH_2)_3$- wherein R_4 is as defined above; or

f) isopropyl optionally monosubstituted in 1-position with (C_{1-3})hydroxyalkyl;

in free form or in acid addition salt form.

4. A compound according to claim 2 (a **compound Is**), wherein R is R^s, which is:

a) $R_1^sR_{1a}^s(CH_2)_{ms}$- wherein R_1^s is pyridinyl optionally mono- or independently disubstituted with chlorine, trifluoromethyl, cyano or nitro; pyrimidinyl optionally monosubstituted with chlorine or trifluoromethyl; or phenyl;
R_{1a}^s is hydrogen or methyl; and
ms is 2 or 3;

b) (C_{3-12})cycloalkyl optionally monosubstituted in 1-position with hydroxymethyl;

c) $R_2'(CH_2)_{ns}$- wherein either

R_2' is phenyl optionally mono- or independently di- or independently trisubstituted with halogen, alkoxy of 1 or 2 carbon atoms or phenylthio monosubstituted in the phenyl ring with hydroxymethyl; (C_{1-6})alkyl; 6,6-dimethylbicyclo[3.1.1]hept-2-yl; pyridinyl; naphthyl; cyclohexene; or adamantyl; and ns is 1 to 3; or

R_2' is phenoxy; and ns is 2;

d) (3,3-diphenyl)propyl;

e) $R_4'(CH_2)_{ps}$ wherein R_4' is 2-oxopyrrolidin-1-yl or isopropoxy and ps is 2 or 3;

f) isopropyl optionally monosubstituted in 1-position with hydroxymethyl;

g) R_5' wherein R_5' is: indanyl; a pyrrolidinyl or piperidinyl moiety optionally N-substituted with benzyl; bicyclo[2.2.1]hept-2-yl; 2,6,6-trimethylbicyclo-[3.1.1]hept-3-yl; adamantyl; or (C_{1-8})alkyl optionally mono- or independently disubstituted with hydroxy, hydroxymethyl or phenyl;

in free form or in acid addition salt form.

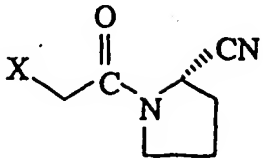
5. The compound according to claim 2 wherein R is 2-[(5-cyanopyridin-2-yl)amino]ethyl, i.e. 1-[2-[(5-cyanopyridin-2-yl)amino]ethylamino]acetyl-2-cyano-(S)-pyrrolidine, in free form or in acid addition salt form, especially in dihydrochloride acid addition salt form, or a compound according to claim 2 which is of formula I wherein R is either

- 2-[(5-chloropyridin-2-yl)amino]ethyl, or
- (1-hydroxymethyl)cyclopent-1-yl, or
- 2-[(5-nitropyridin-2-yl)amino]ethyl, or
- 3-(isopropoxy)propyl,

in free form or in acid addition salt form.

6. A process for the preparation of a compound according to claim 1 which comprises coupling a reactive (2-cyanopyrrolidino)carbonylmethylene compound with an appropriate substituted amine or, for the preparation of a compound according to claim 2, which comprises

reacting a compound of formula II



II

wherein X is a reactive group,

with a compound of formula III

NH_2R III

wherein R is as defined in claim 2,

and recovering the resultant compound in free form or in acid addition salt form.

7. A pharmaceutical composition comprising a compound according to claim 1 in free form or in pharmaceutically acceptable acid addition salt form, together with at least one pharmaceutically acceptable carrier or diluent.

8. A compound according to claim 1 in free form or in pharmaceutically acceptable acid addition salt form, for use as a pharmaceutical.

9. Use of a compound according to claim 1 in free form or in pharmaceutically acceptable acid addition salt form in the preparation of a medicament for inhibiting DPP-IV or treating conditions mediated by DPP-IV.

10. A method of inhibiting DPP-IV, or of treating a condition mediated by DPP-IV, which comprises administering a therapeutically effective amount of a compound according to claim 1 in free form or in pharmaceutically acceptable acid addition salt form to a patient in need of such treatment.

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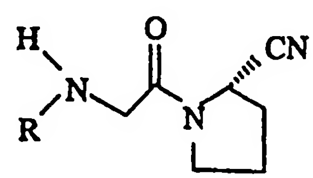
(54) Title: N-SUBSTITUTED 2-CYANOPYRROLIDINES

(57) Abstract

N-(N'-substituted glycyl)-2-cyanopyrrolidines, e.g. the compounds of formula (I) wherein R has various significances, are novel. They inhibit DPP-IV (dipeptidyl-peptidase-IV) activity. They are therefore indicated for use as pharmaceuticals in inhibiting DPP-IV and in the treatment of conditions mediated by DPP-IV, such as non-insulin-dependent diabetes mellitus, arthritis, obesity, osteoporosis and further conditions of impaired glucose tolerance.



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INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/06125

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D207/16 C07D401/12 C07D403/12 A61K31/40 A61K31/44
A61K31/505

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 90 12005 A (YOSHITOMI PHARMACEUTICAL INDUSTRIES, LTD.) 18 October 1990 see page 39, compounds 19, 20, 22, 24 see abstract ---	1,7
A	EP 0 172 458 A (SUNTORY LTD.) 26 February 1986 see claims 1,4 ---	1,7
A	EP 0 115 639 A (HOECHST AG) 15 August 1984 see claim 1 ---	1
A	EP 0 132 580 A (HOECHST AG) 13 February 1985 see page 10, line 30 - page 11, line 3 -----	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
5 May 1998	25.05.98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Hass, C

INTERNATIONAL SEARCH REPORT

I national application No.
PCT/EP 97/06125

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 10
because they relate to subject matter not required to be searched by this Authority, namely:

Remark: Although claim 10 is directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest

[ ] No protest accompanied the payment of additional search fees

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interna al Application No
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